FDA Executive Summary

Prepared for the May 13, 2014 Meeting

of the

Ophthalmic Devices Panel of the Medical Devices Advisory Committee

Contact Lens and Care Product Guidance Documents

A. Introduction

Contact lenses and accessories to contact lenses such as contact lens care products are regulated as medical devices and are used by more than 40 million consumers in the United States.[1] Although the FDA has created and used a number of tools (i.e., guidance documents and recognized standards) for safe and effective products to be introduced into the marketplace, new concerns have emerged in recent years. In 2006, suspected cases of *Fusarium* keratitis were reported to the Centers for Disease Control (CDC) and FDA, resulting in the voluntary recall of a Multipurpose Solution (MPS). In 2007, cultures from 138 patients that tested positive for *Acanthamoeba* keratitis (AK) resulted in the voluntary recall of an additional MPS suspected to be associated with this infectious outbreak. However, AK cases persist despite the voluntary recall of product.[2] Therefore, to better determine reasons for the persistent increase, the CDC initiated a new investigation working with the FDA in 2011.[2] In addition, FDA also found that changes in dimensions of silicone hydrogel lenses exposed to particular contact lens care products could result in incompatibilities denoted as precautions in the labeling. These findings further underscore our need to determine a root cause for lens/solution incompatibilities to better understand lens/solutions interactions, to develop more effective preclinical testing to prevent potential ocular infections, and to continue our efforts to educate consumers.

FDA undertook a series of research projects in 2008 to further enhance contact lens safety, the results of which were published in *Eye and Contact Lens*.[3] Our research led to the development of a novel grouping system for silicone hydrogel contact lenses which can be used to better identify lens-solution incompatibilities.[4] In addition, prior to our research no consensus had been reached regarding an appropriate microbiological test method for *Acanthamoeba*. That, combined with an urgent need to include this organism as part of the preclinical test panel for MPS, resulted in the development of a protocol for optimizing conditions for testing MPS efficacy against this organism.[5] Based on information obtained from the previous outbreaks, we also reassessed current biocompatibility recommendations, as previous recommendations did not include an assessment of lens/solution interactions. Lenses were previously classified for biocompatibility testing as external communicating devices. However, we now recommend that these devices be categorized as permanent contact devices. In addition, we have proposed novel lens/solution compatibility testing. Members of the Division of Ophthalmic and Ear, Nose and Throat Devices (DOED) plan to revise the 1994 guidance document for daily wear contact lenses (*Premarket Notification 510(k) Guidance Document for Daily Wear Contact Lenses*)[6] and the 1997 guidance document for Contact Lens Care Products (*Guidance for Industry: Premarket Notification (510(k)) Guidance Document for Contact Lens Care Products)*[7] to reflect our current thinking regarding tests needed for clearance for contact lenses and contact lens care product solutions. In addition, we plan to share the results of our research with standards organizations for improved pre-market testing and evaluation of contact lenses and care products. We anticipate that our efforts will result in a significant public health impact based on our proposed changes and the number of patients that may be affected by these changes.

In the following, we include a brief look at pre-clinical testing, clinical and labeling issues that serve as the basis for discussion with respect to proposed modifications to our guidance and are relevant to our mission to promote safety within this patient population. In addition, our collaborations with the CDC to address the ongoing concerns of *Acanthamoeba* keratitis infection and safe use of these devices will be presented to further underscore the need to update our guidance.

B. Preclinical - Chemistry/Materials

The FDA reviews premarket testing performed by manufacturers to ensure that lens materials packaged in solution or used in conjunction with contact lens care product solutions are safe and effective. In the past, lens material and solution formulations were less complex and methodologies to identify lens-solution incompatibilities were adequate. However, over the past 10 years, outbreaks of infectious microbial keratitis, new and emerging lens and solution technologies as well as evidence of potential lens-solution incompatibilities have resulted in an increased effort to update our testing paradigm to reflect current knowledge and thinking and to ensure that current products remain safe and effective.[8] The FDA currently recognizes a lens material grouping system that allows representative lenses to be used in pre-market lens care product testing for lens-solution incompatibilities. The current grouping system was developed over 20 years ago and is still used today to evaluate lens-care product compatibility for "conventional" poly (2-hydroxyethyl methacrylate (HEMA)) hydrogel lenses. From this testing, any lens-solution incompatibilities identified were listed in the labeling. The following grouping system when used in conjunction with established criteria for identifying solutions that may irreversibly alter lens dimensions and power has been effective for evaluating and predicting potential incompatibilities with poly(HEMA) lenses.

Conventional Hydrophilic Material Groups ("-filcon"):

Group	Description
I	Low Water Content (<50%), Nonionic*
II	High Water Content (≥50%), Nonionic*
III	Low Water Content (<50%), Ionic*
IV	High Water Content (≥50%), Ionic*

*Being ionic in pH = 6.0 - 8.0.

However, with the advent of newer silicone hydrogel materials, incompatibilities began to emerge that were not predicted by the conventional grouping system.[9,10] One cause for the lack of predictability was the inadequate characterization of newer lens materials. Therefore, as part of an ongoing research initiative, FDA decided to better characterize silicone hydrogel lens materials.

The following additional silicone hydrogel groups were added to account for the different material features compared to poly(HEMA) lenses, such as siloxane polymer hydrophobicity, surface treatments, and the use of semi-interpenetrating polymer networks.[4]

Silicone Hydrophilic Material Groups ("-filcon"):

Group	Description
V-A	No Water Specification, Ionic*
V-B	High Water Content (≥50%), Nonionic*
V-C	Low Water Content (<50%), Nonionic*, Hydrophilic Mon. only
V-C_m	Low Water Content (<50%), Nonionic*, Surface Treated (ST)
V-C_r	Low Water Content (<50%), Nonionic*, Non-ST, Semi-interpenetrating network

*Being ionic in pH = 6.0 - 8.0.

The new grouping system encompasses attributes of the old conventional system and adds criteria that can better evaluate the newer silicone hydrogel lenses. This feature of the new system is fortuitous since the old system could accurately predict whether lens material would adsorb hydrophilic preservatives from care product solutions. The implications of preservative adsorption or uptake was not completely appreciated until reports from the literature began to surface that excessive preservative uptake by lens materials could compromise the disinfection efficacy of care product solutions.[11,12] As part of FDA's research efforts, we sought to confirm these reports. We concluded that certain lens materials when used in conjunction with solutions containing certain preservatives may compromise disinfection efficacy of the solution.[13,14] This consequence of preservative uptake is not currently evaluated in our premarket testing of contact lenses and care product solutions. Therefore, we propose to update our guidance to recommend a simulated test where manufacturers should demonstrate that, when incubated in a care product solution, representative lenses do not decrease the concentration of preservative below the specified concentration range The Panel will be asked whether our proposed grouping scheme for silicone hydrogel lenses is adequate to mitigate prior concerns regarding dimensional tolerance and incompatibility. In addition, Panel input will be sought regarding whether the acceptance criterion for our proposed test should account for patient non-compliance and ways to include information regarding incompatible lens/solution combinations in the labeling.

C. Preclinical - Microbiology

In 2009, FDA held a workshop co-sponsored by the American Academy of Ophthalmology (AAO), American Academy of Optometry (AAO), American Optometric Association (AOA), and Contact Lens Association of Ophthalmologists (CLAO) to discuss microbiological testing of contact lens care products. Among topics discussed at the workshop were factors that could impact test disinfection efficacy test methods for multi-purpose solutions against *Acanthamoeba* species. It was concluded that the strain type, the life cycle stages, growth method, and encystment technique were all important factors in developing the most robust protocol in testing solutions. As a result, FDA examined these factors to consider when developing these test methods and published a draft protocol.[5] It was determined that at least two different strains in cyst form would be appropriate for disinfection efficacy testing. In addition, FDA's research demonstrated that the organism presents more of a challenge when it is grown on agar seeded with bacteria and encysted by the starvation method .[5]

FDA research has focused on the importance of testing MPS-contact lens interactions using a real-world noncompliance situation in which solution reuse occurs. The effect of the presence of 6 different silicone hydrogel lens materials and 2 conventional hydrogel lens materials on the concentration of the microbiocidal agent in the MPS and the microbiocidal activity of the MPS were evaluated. A MPS containing polyhexamethylene biguanide (PHMB) was tested using *Staphylococcus aureus* and *Fusarium solani* and a MPS containing polyquanternium-1 and myristamidopropyl dimethylamine was tested using S. aureus. PHMB concentrations in the MPS were significantly reduced in the presence of etafilcon A, balafilcon A, and polymacon lenses after only 6 hours of soaking in the MPS.[13,14] Microbiocidal activity for S. aureus was reduced for MPS exposed to etafilcon A lenses and microbiocidal activity against F. solani was reduced for MPS exposed to 7 of the 8 lens material types tested. The concentration of polyquaternium-1 and myristamidopropyl dimethylamine was reduced only slightly in the presence of contact lenses and no adverse effect on the microbiocidal effect against S. aureus was noted.[15] These studies suggest the importance of testing all lens care solutions in the presence of lenses. The current FDA recognized standard ISO 14729:2001/Amend. 1: 2010 notes that manufacturers should consider evaluating MPS in the presence of contact lenses. However, the standard does not specify including this parameter. Therefore, FDA is proposing incorporating this and other specific parameters (i.e., soil, longer soak times) into our guidance. The Panel will be asked to provide input regarding this proposal.

D. Clinical Issues

In addition to the preclinical and clinical performance issues of various types of lens products with specific categories of contact lenses, the role of the consumer's care of contact lenses must also be considered. Consumer behaviors underlying clinical contact lens complications have been addressed extensively in the literature (Please see Attachment C for information regarding patient labeling principles, instructions for use and warning examples to address consumer misuse issues. In addition, links to the FDA's Contact Lens Website, the "Guidance on Medical Device Patient Labeling", the "Guidance Document for Contact Lens Care Products", and the "Guidance Document for Daily Wear Contact Lenses" are attached for reference). [6,7,16, 23, 24]

80% of all contact lens wear complications are the result of noncompliance with wear and care regimens according to Ky (et al.) in their 1998 study.[17] Of note, the consumer's perception of their own compliance behavior is fundamental to minimizing and/or preventing these complications.

Various studies regarding contact lens care compliance have verified this finding. In 2004, DiMatteo published a study analyzing general medical compliance.[18] His study revealed that in 2000, there were 759.3 million physician visits. 188.3 million of these visits resulted from patients not following their physician's orders. This translates to a noncompliance rate of 24.8% for general medical care. Donshik et al., identified that complexity of treatment, frequency of duration, and the cost of the regimen are the major factors that affect contact lens compliance.[19] In Olivera's self-evaluation of contact lens care on college students and health care workers, it was found that 54.2% considered themselves poor wearers.[20] Of these, 44.3% claimed that they were poor wearers because of their inadequate cleaning of lenses or the lens case. Another 15%

admitted to general medical noncompliance. Regarding contact lens procedures, 79.1% responded that they fail to implement contact lens care procedures and another 30% claim that their noncompliance is due to lack of knowledge or being poorly prepared to care for their lenses.

Collins found a noncompliance rate of 74% in adult wearers who had worn lenses for an average of 2.6 years.[21] This study also found the components of noncompliance to be lack of understanding, improper usage of lens care products, and poor hand hygiene. This study population had many symptoms and complaints yet they did not perceive themselves as noncompliant. Likewise, Turner found a noncompliance rate of 91%. Turner's results focused on multipurpose solutions and found that the failure rate was high despite the ease of use of the MPS.[22] Since non-compliance is so wide-spread, the Panel is asked to comment on whether manufacturers of CLCP should account for non-compliance in their premarket testing along with factors that should be included (e.g., topping off, more than and less than recommended soak times, etc.).

E. Use of Water with RGP Lens Care

Although exposure to water while wearing contact lenses has been a known risk factor specifically for *Acanthamoeba* keratitis, many Rigid Gas Permeable (RGP) lens care regimens continue to include the use of water.[25] The early association of *Acanthamoeba* keratitis will be revisited, leading up to the *Acanthamoeba* keratitis outbreak in 2007. [26, 27, 28] A labeling presentation will revisit the recommendations that emerged from the 2008 FDA Ophthalmic Panel Meeting, specifically those changes pertaining to the use of water with contact lenses, and the addendum to the 510(k) Contact Lens Care Labeling Guidance that was subsequently published.[29] Published case histories will be reviewed [25, 30, 32, 33] in which the outcomes demonstrate that contact lens related *Acanthamoeba* keratitis continues to be a small but significant cause of infection.[31] Because of the continued risk of undesirable outcomes that can result, alternatives to the use of water in conjunction with the care of RGP lenses must be considered. Therefore, the Panel is asked to review and discuss these alternatives.

F. CDC/FDA Efforts and Collaboration

The CDC is invited to give a presentation at this Panel meeting. Relevant publications may be found in Attachment E [34, 35, 36, 37].

Bibliography

Attachment A – Introduction

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Attachment B – Pre-Clinical

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Attachment C – Clinical

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Attachment D - Labeling

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Attachment E – CDC

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